PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/002362	07.03.2005	11.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D471/04, A61K31/437, A61P11/06, A61P35/02, A61P37/08

Applicant
ACTELION PHARMACEUTICALS LTD

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Papathoma, S

Telephone No. +49 89 2399-7536

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The application refers to tetrahydropyridoindole derivatives of the formula I suitable as CRTh2 receptor antagonists, to pharmaceutical compositions comprising at least one of them, and to their use as medicament and for the preparation of a medicament for the prevention or treatment of prostaglandin mediated diseases.

Reference is made to the following documents:

D1: EP-A-1 505 061 (SHIONOGI & CO., LTD) 9 February 2005 (2005-02-09), corresponding to WO03097598 (D1') published on the 27.11.2003 (* see Re Item VI)

D2: GB-A-2 388 540 (BAYER AG) 19 November 2003 (2003-11-19)

D3: WO 03/101981 A (ASTRAZENECA AB; BIRKINSHAW, TIMOTHY; BONNERT, ROGER; COOK, ANTHONY; RA) 11 December 2003 (2003-12-11)

D4: JP 09 216882 A (ISUKURA SANGYO KK) 19 August 1997 (1997-08-19)

1) Article 33(2) PCT

Document D1' discloses in table 18 compounds Id-1, Id-2 and Id-3 differing from the claimed entities in that the nitrogen of the tetrahydropyrido-moiety is substituted with an (hetero-)aryl-sulphonyl-substituent instead of eg. (hetero-)aryl-carbonyl substituent as presently claimed.
D2 refers to the structurally similar Ramatroban.
D3 discloses indole-1-acetic acid derivatives suitable as CRTh2 receptor antagonists.
D4, although discloses in pages 50 and 56 formulae I.1 and I.1.2 respectively, which overlap with formula I of the present application, does not explicitly disclose compounds that fall under the presently claimed subject matter.
The subject matter of the present application is thus acknowledged to fulfill the requirements of Article 33(2) PCT.

2) Article 33(3) PCT

The problem outlined in the present application is to provide compounds, suitable as CRTh2 receptor antagonists. As the prior art (documents D1', D2 and D3) has already dealt with this problem, the actual technical problem may be seen in the provision of **further** compounds

suitable as CRTh2 receptor antagonists.

Alternative solutions to a known technical problem can be considered as inventive when it can be shown that they do not derive from the prior art in an obvious manner and that they indeed solve the problem eventually showing an unexpected effect.

With respect to the question whether the subject matter of the present application provides a "real" solution to the technical problem mentioned above, the biological tests provided in pages 66-70 and in particular tables 13 and 14 show that the disclosed examples do have the claimed activity.

With respect to the information given from the prior art and the question whether the solution provided by the present application can be derived in an obvious manner, this Authority considers the claimed compounds as structurally close related to the entities disclosed in the prior art, and that the minor modification, which distinguishes them from the latter can be regarded as part of the synthetic routine of the person skilled in the art when looking for alternative solutions:

document D1', which can be considered as the closest prior art, discloses structurally closest related compounds with the same activity, differing from the claimed entities in that the nitrogen of the tetrahydropyrido-moiety is substituted with an (hetero-)aryl-sulphonyl-substituent instead of eg. (hetero-)aryl-carbonyl substituent as presently claimed. However, a carbonyl and a sulphonyl group are often exchanged by the person skilled in the art when looking for alternative solutions.

Since this variation (carbonyl- / sulphonyl-group) belongs to the common practice of the person skilled in the art when looking for an alternative solution to a known and solved chemical problem, and on the basis of the information given by the documents D1', D2 and D3 for the structural features of compounds suitable as CRTh2 receptor antagonists, the subject matter of the present application is considered as not to involve inventive ingenuity, and therefore does not fulfill the requirements of Article 33(3) PCT.

However, reconsideration regarding the evaluation of the inventive merit of the subject matter of the present application, would only be possible if it could be shown that the claimed subject matter shows unexpected effects with respect to the closest prior art. Consequently, in that

case, further evidence would be needed, where the properties of the claimed compounds are compared with those of the structural more related compounds from D1' .

Re Item VI

Certain documents cited

Although document

D1: EP-A-1 505 061 (SHIONOGI & CO., LTD) 9 February 2005 (2005-02-09)

is published after the priority day and before the filing day of the application, and therefore can not be considered as prior art document according to the Article 33(2) PCT, it serves as a translation of the corresponding WO03097598 published on the 27.11.2003, which is a prior art document according to the Article 33(2) PCT.